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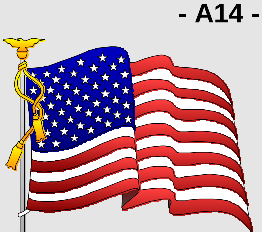
ISSUE HIGHLIGHTS



Remember Memorial Day
May 26, 1997

Treatment of Benign Prostatic Hyperplasia

Since the initial Tri-Service Formulary (TSF) was approved in November 1993, the PEC has completed seven disease state reviews resulting in changes to the TSF. This disease state review of the treatment of symptomatic benign prostatic hyperplasia (BPH) marks the eighth revision to the TSF. This PEC Update contains the TSF changes, cost-effectiveness model, treatment guidelines, preferred drug list, and drug use evaluation (DUE) criteria for the treatment of BPH.

Executive Summary

Background

Symptomatic benign prostatic hyperplasia (BPH) causes one out of four men under 80 years old to seek medical care. Treatment for this disease includes the “gold standard” of transurethral resections of the prostate (TURP) and/or pharmacotherapy using androgen-suppressive therapy (e.g., finasteride) or alpha-adrenergic blockers (e.g., doxazosin, prazosin, terazosin). It has been estimated that the annual cost for TURPs alone is between $2 billion and $5 billion; however the number of TURPs performed annually has declined since 1987. This decline can be attibuted to increased utilization of pharmacotherapy for treatment of BPH. Department of Defense (DoD) costs for treatment of BPH will undoubtedly increase since the elderly are one of the fastest growing populations in the United States.

Methods

This pharmacoeconomic analysis of BPH evaluates finasteride, doxazosin, prazosin, terazosin, and surgery which are considered appropriate treatment for BPH by the Agency for Health Care Policy and Research (AHCPR). The AHCPR guideline indicates that all the alpha-blockers have the same efficacy.

The data used in this study were derived from AHCPR guidelines and current literature. Additionally, a panel of clinicians (urologist, internist, and family practitioner) was convened to develop and validate data unavailable in clinical literature. Pertinent AHCPR data included the initial evaluation of the male presenting with signs characteristic of BPH, follow-up symptom assessment based on American Urological Association (AUA) symptom scoring, diagnostic tests, and treatment recommendations. These data served as the basis for the study. The assessment categorized the patient as having mild or moderate BPH symptomatology. Therapy was based exclusively on a patient's subjective symptomology scoring. It was assumed that only when the patient became symptomatic was drug therapy to be initiated.

A decision tree was developed to conduct a cost-effectiveness analysis from the perspective of the DoD as payer of the health care benefit. The 36 consecutive month decison tree consisted of the aforementioned drugs as initial therapy following an unsucessful period of watchful waiting. All therapy failures received secondary interventions including TURP.

This study applies only to males greater than 50 years of age with classic symptoms of prostatism and no other confounding comorbidities. The model incorporated pertinent costs and assumptions for both medical and surgical treatment of BPH. Because this study was a cost-effectiveness analysis, costs were expressed in dollar terms and outcomes in non-monetary terms (i.e., clinical effectiveness). For current economic applicability, dollar values assigned to health care resources were taken from standardized 1994 payment schedules used by third party payers. Additionally, because the study extended beyond 1 year, a standard discounting rate of 5% was utilized, which is approximately the inflation-adjusted historical interest rate.

Mathematically, the model was designed to force specific paths within the decision trees. At no point in the decision trees was a choice made between a TURP and a ReTURP. The model did not allow the same class of drug therapy to be used more than once in any path nor did there exist the possibility of reverting back to watchful waiting after pharmacotherapy was initiated.

A Monte Carlo simulation was used for a sensitivity analysis on all variables. The simulation consisted of multiple trials of the model while assigning random values, based on a particular distribution as determined by the literature for each variable. In this Monte Carlo simulation the cost figures were allowed to vary ±10%, thus, permitting a conservative 20% range about the point estimate. The efficacy rates were allowed to vary 2% more than the 90% confidence intervals based on the AHCPR guidelines. In addition, the Monte Carlo sensitivity analysis was used to evaluate the effect of changes in results for data that were not available in the literature.

Results
The analysis demonstrated the alpha-blockers to be more cost-effective than finasteride. Of the alpha-blockers, prazosin was the most cost-effective with a cost-effectiveness of $1154.81 per symptomatic relief of BPH.

Of a given population of males greater than 50 years old with classic symptoms of prostatism and no confounding comorbidities, the model predicts that 70.3% of the patients will be successfully treated with prazosin at a cost of $578.15 per patient. Additionally, 19.90% of the patients would be successfully treated with finasteride at a cost of $1,426.53 per patient; 8.62% would be successfully treated with TURP at a cost of $4,321.36 per patient; and 0.59% would be successfully treated with ReTURP at a cost of $7,650.54 per patient. Based on the data from treatment with prazosin, finasteride, TURP, and ReTURP above, the total of successfully treated patients in any given population would be 99.41%.

Tri-Service Formulary Selection
The results of the disease state analysis of benign prostatic hyperplasia demonstrate that the alpha-blockers are the most cost-effective pharmacologic therapy, with prazosin the most cost-effective alpha-blocker. Based on this analysis, prazosin is added to the Tri-Service Formulary. Terazosin, the next most cost-effective alpha-blocker, is currently on the TSF for hypertension, but should be considered for those patients with BPH who cannot tolerate prazosin. Terazosin will remain on the TSF.

TSF Revisions Resulting from the Benign Prostatic Hyperplasia Review

AHFS Category*		Action
24:08	***Hypotensive Agents***	
	Prazosin 1 mg, 2 mg, 5 mg capsules	Add
	Terazosin capsules	Retain

* AHFS = American Hospital Formulary Service

A Pharmacoeconomic Analysis of Patients with Symptoms of Benign Prostatic Hyperplasia

Introduction

Benign prostatic hyperplasia (BPH) is generally considered a disease of elderly males, although it has been noted in 10% of men 25 to 30 years of age while increasing to 90% by 85 years of age.[1] Recent data demonstrated that the mean age for the development of symptomatic disease is approximately 60 years for blacks and approximately 65 years for Caucasians.[2] BPH is the most common cause of obstruction to urinary outflow in men.[2] Four conditions are associated with the disease process: (1) anatomic prostatic hyperplasia; (2) symptoms of prostatism (e.g., hesitancy initiating voiding, incomplete emptying); (3) urodynamic presence of obstruction; and (4) detrusor muscle response to obstruction.[1] Current estimates suggest one in every four men in the U.S. will be treated for relief of these conditions by 80 years of age.[1] In addition to medical treatment, the rates of transurethral resections of the prostate (TURP) for all indications in a national sample of Medicare beneficiaries were roughly 25, 19, and 13 per 1000 for men over the age of 75, 70 to 74, and 65 to 69, respectively.[3] The number of TURPs performed annually in the U.S. has decreased since 1987, presumably due to changes in treatment patterns.[3] Other sources suggest 25% to 30% of all men will eventually require prostatic surgery for relief of clinically severe BPH.[4]

In 1994 estimates of costs (in US dollars) associated with TURPs ranged from $2 billion to $5 billion annually.[1,5,6] A 1-year retrospective study of 1,982 public hospital patients and 1,128 private patients with BPH in New Zealand showed TURP was the most common treatment of BPH, and was associated with costs (in US dollars) of $8.73 million (direct) and $2.18 million (indirect).[7] Another study found primary care costs (in US dollars) in the U.K. and England ranged between $4.65 to $5.47 million. A subgroup analysis demonstrated inpatient costs (in US dollars) totaled $22.78 million.[8]

The pathophysiology of BPH is not well understood; however, the presence of testes and the process of aging are two necessary elements.[2] It must be noted that a direct relationship between obstruction and prostatic size does not exist.[2,9-11] Regardless of the underlying physiology, the obstructive process precipitates irritative symptoms that manifest as increased frequency of urination, nocturia, urgency, and urge incontinence.[9,10] Further obstruction results in a dimunition in the caliber and force of the urinary stream, hesitancy of urination, postvoid dribbling, the sensation of incomplete emptying, and possible urinary retention. Obstruction may eventually result in hydronephrosis, urinary tract infection, stone formation, and possibly, renal failure. All of these potential indicators are common presenting symptoms of BPH.[9,10]

BPH is clinically treated as a presumptive diagnosis based on symptoms of prostatism.[1] Although symptomatology scales (e.g., Boyarsky Symptom Scale) have been employed in clinical trials,[12-14] only the American Urological Association (AUA) Symptom Index is currently endorsed by the Agency for Health Care Policy and Research (AHCPR).[1]

Although surgical intervention remains the "gold standard" for the treatment of BPH, androgen-suppressive therapy (e.g., finasteride), thought to target the static component of the disease, and alpha-adrenergic blockers (e.g., doxazosin, prazosin, terazosin), thought to target the bulk/dynamic components of BPH, are considered worthwhile treatments.[1,14] The pharmacology and pharmacokinetics of these drugs as well as general pharmacoeconomic principles have been extensively reviewed elsewhere.[15-25]

Pharmacoeconomic data for BPH are limited despite abundant clinical literature evaluating various therapies. A recent pharmacoeconomic analysis evaluated the cost-effectiveness of finasteride, terazosin, and TURP.[26] The authors concluded that pharmacotherapy was more cost-effective than TURP and that terazosin was the more cost-effective therapy of the two pharmacological agents evaluated. It is well established that the other two alpha blockers, prazosin and doxazosin, provide equal efficacy compared to terazosin.[1] Although there are theoretical arguments for the superiority of terazosin when compared to the other two alpha blockers, a critical review of clinical trials fails to substantiate any significant difference between them, except in convenience of dosing.[27-34]

There is clear consensus that watchful waiting is the most appropriate first line therapy for the majority of patients.[1] After failing that, it appears that pharmacotherapy is more cost-effective than surgical intervention and that comparisons between finasteride and terazosin have shown the latter to be more cost-effective.[26] This developing consensus is complicated by two difficulties. First, cost-effectiveness is a moving target. The costs used will impact the results. The study by Lowe and colleagues used wholesale drug costs.[26] The results may be different in those situations where drug costs are significantly below wholesale costs. Second, and more importantly, no study has evaluated the cost-effectiveness of all three alpha-blockers compared to finasteride in the treatment of BPH. This limits the ability of physicians to determine which medication should initially be chosen when deciding to treat a patient after watchful waiting fails. This study evaluates all relevant treatment options for BPH from the perspective of the Department of Defense as payer of the healthcare benefit.

Methods

The majority of clinical data for finasteride, doxazosin, prazosin, terazosin, and surgery was obtained from the AHCPR Clinical Practice Guideline.[1] Pertinent AHCPR data included the initial evaluation of the male presenting with signs characteristic of BPH, follow-up symptom assessment based on AUA symptom scoring, diagnostic tests, and treatment recommendations. These data served as the basis for the study. The assessment categorized the patient as having mild or moderate BPH symptomatology. As recommended with this particular disease, therapy was based exclusively on the patient's subjective sympto-matology scoring. It was assumed that only in the case that the patient became symptomatic was drug therapy to be initiated. A panel of clinicians (urologist, internist, and family practitioner) was used to validate the model and data not available in the clinical literature, such as the number of prostate specific antigen (PSA) tests a clinician would attain with a particular BPH patient.

A decision tree was used to evaluate the cost-effectiveness of drug therapy from the perspective of the DoD as payer. The 36 consecutive month decision tree consisted of the aforementioned drugs as initial therapy following an unsuccessful period of watchful waiting. As an example, a **portion** of the decision tree process is illustrated in Figure 1. Therapy was continued toward a successful response. All therapy failures switched to secondary interventions including TURP.

Government prices were used in the model for drug costs; outpatient office visits were taken from Current Procedural Terminology (CPT) codes and Medicare Resource-based Relative Value Scale (RBRVS); and inpatient surgical procedure costs were based on Medicare Diagnosis Related Groups (DRGs). Because this study was a cost-effectiveness analysis, costs were expressed in dollar terms and outcomes in non-monetary terms (i.e., clinical effectiveness). Costs were valued in 1994 dollars. Additionally, because the study extended beyond 1 year, a discount rate of 5% was used, which is approximately the inflation-adjusted historical interest rate. Table 1 includes an explanation of the cost variables employed in the analysis. Mathematically, the model was designed to force specific paths within the trees:

- use of a pharmacological agent = 1 minus TURP
- use of a pharmacological agent = 1 minus ReTURP.

The above equations allowed the model to follow specific paths of therapy according to TURP and ReTURP values of "all or nothing" (i.e., 0 or 100). This strategy was effective because there was no point in the decision trees where a choice is made between a TURP and a ReTURP. The model did not allow the same class of drug therapy to be used more

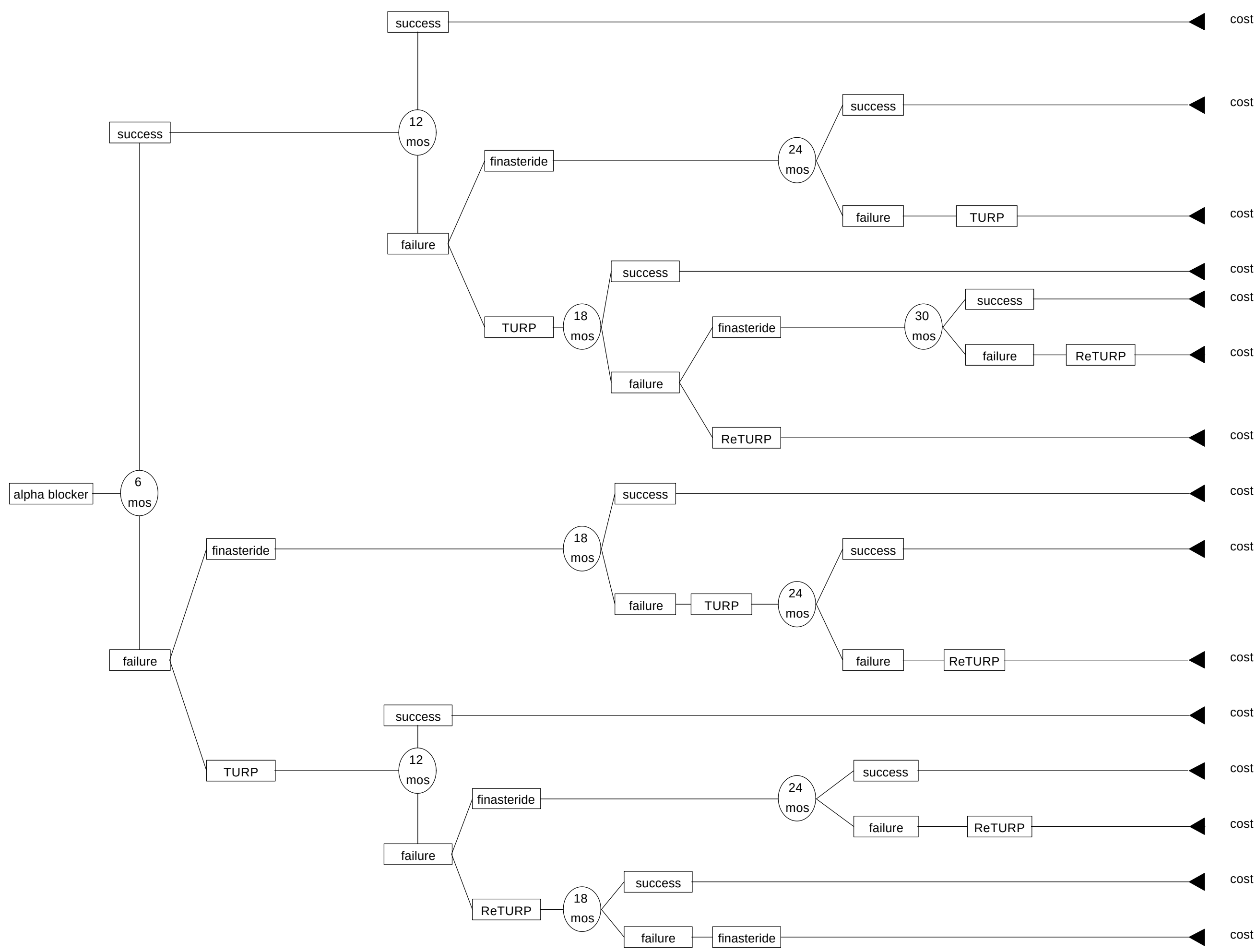


Figure 1. Alpha-blocker decision tree to illustrate the pharmacoeconomic model. The finasteride decision tree is constructed in a similar manner.

than once in any path nor did there exist the possibility of reverting back to watchful waiting after pharmacotherapy was initiated.

Table 2 breaks down the cost associated with initiating and continuing BPH therapy as used in the model. The first six months of therapy includes the cost of the drug plus the cost of provider visits and necessary laboratory tests to initiate and achieve the target dose. Doxazosin was titrated to a maximum dosage of 8 mg every day; terazosin was titrated to 10 mg every day; prazosin was titrated to 5 mg twice daily; and finasteride was not titrated, but initiated and maintained at 5 mg every day. The titration schedules resulted in four general MD visits (OV1GP) for doxazosin and terazosin and 3 visits (OV1GP) for prazosin.

Costs of the drugs were based on once daily dosing for doxazosin and terazosin and twice daily dosing for prazosin. Compliance was assumed equal among all therapies,[35-37] and drug therapy was started only after an initial period of watchful waiting. An assumption was made that clinical efficacy would be evaluated 6 months after drug therapy and 6 months following surgery. The schedule of follow-up visits, labs, procedures, etc. was adopted from the AHCPR Clinical Practice Guidelines.[1]

A Monte Carlo simulation was used for sensitivity analysis on all variables. The simulation consisted of multiple trials of the model while assigning random values, based on a particular distribution and spread, to each variable. In this simulation the cost figures were allowed to vary ± 10%, thus, permitting a conservative 20% range about the point estimate. The efficacy rates were allowed to vary 2% more than the 90% confidence intervals based on the AHCPR guidelines (Table 3). In addition, the sensitivity analysis was used to evaluate the effects of changes in data that were not available in the literature. Table 3 provides point estimates and ranges used in the sensitivity analysis for efficacy rates and costs.

Clinical success was defined as symptomatic improvement requiring no additional intervention with the exception of routine, standard-of-care follow-up. Clinical failure was defined as a lack of clinical improvement or clinical deterioration that required additional therapeutic intervention. Insufficient data were available to adequately compare mortality between the different therapies. Thus, costs associated with treatment mortality were not incorporated into the model. If a patient was not successful after two TURPs following unsuccessful trials of an alpha-blocker or finasteride, the patient was not restarted on drug therapy. Success of drug therapy for subsequent interventions was assumed to be independent of the previous intervention. The overall analysis was structured into dichotomous outcomes. The subjective relief of symptoms and associated probabilities are based on global patient improvement. The AHCPR probabilities[1] for successful symptomatic relief were median probabilities with 90% confidence intervals which were extended ± 2% (Table 3).

Appropriate physician visits, drug costs (including titration, if applicable), and lab costs were allotted to each 6 month period of treatment. Model assumptions included drug therapy only during general practitioner care, a single prostate specific antigen (PSA) measured after failure of watchful waiting, and allocation of serum creatinine (SCr) and urinalysis (UA) measurements throughout the course of the 36 month simulation.

Table 1. Explanation of Variables Included in Model

Variable	Time Incurred	Description
Finasteride cost	Duration of therapy	No titration; 5 mg/d = $189.80/6 months
TURP cost	At surgery	$3838.47
ReTURP cost	At surgery	$3838.47
Terazosin cost	Duration of therapy	$81.90/titration; 10 mg/d = $81.90/6 month
Prazosin cost	Duration of therapy	$23.52/titration; 5 mg BID = $25.48/6 month
Doxazosin cost	Duration of therapy	$92.82/titration; 8 mg/d = $94.64/6 month
Pre-surgery urologist visit (OV1Urol) 30 min visit	Before TURP and ReTURP, if applicable	$61.87
Post-surgery urologist visit (OV2Urol) 15 min visit	After TURP and ReTURP, if applicable	$39.06
General MD titration visits (OV1GP) 10 min visit	Terazosin/doxazosin - 4, prazosin - 3, finasteride - 1	$22.19
General MD 6 month visits (OV2GP) 30 min visit	Every 6 month during drug therapy and after surgery	$31.25
General MD visit 60 minute visit	At pretreatment, 12 month, and 24 months	$104.06
Serum Creatinine (SCr) labs	1 at pretreatment, 12 month, and 24 months	$16.00
Urinalysis (UA) labs	1 at pretreatment, 12 month, and 24 months	$22.00
Uroflowmetry with surgery (URF)	Each surgery	$55.00
Post-void residual urine assessment (PVR)	Each surgery	$95.00
Prostate specific antigen (PSA)	1, at initial treatment	$49.00

Discount Rate (entire 36 month period) = 5.0%; mg/d = milligrams/day; BID = twice daily

Serum creatinine and UA were allocated to each period in order to accrue the respective lab costs over the remaining periods after the initial 6 months of therapy. It was calculated by allocating 3/5 of total SCr costs and 3/5 of total UA costs to each period (three labs allocated over five, 6 month periods). This method enabled the model to assign appropriate costs irrespective of when the actual laboratory costs occurred or which specific path (branch of the decision tree) was followed by a patient in the simulation. If surgery was included in the simulated treatments, a referral was made from the general practitioner to a urologist. At that particular point in the course of therapy, urologist fees were incurred along with a uroflowmetry study and a post-void residual urine assessment. For all successful therapies, continuation costs included only general practitioner follow-up fees, respective drug therapy costs, and SCr/UA allocation per period.

The final cost of each decision tree was based on cumulative costs and the time during which those costs were incurred for multiple possible paths along the decision tree. An annualized discount rate of 5% was applied every 6 months. Drug costs included costs of titration and standard maintenance therapy. Surgical costs were incurred at the time of surgery. Office visits and laboratory tests were standardized to the specific therapies. The adverse drug reactions associated with these drugs are thought to be self-limiting and monetarily inconsequential to the overall health care system. Thus, these costs were not addressed in this study.

Table 2. Costs Associated with Start and Continuation of Therapy

First 6 months of Therapy*		**Subsequent 6 month periods**	
Finasteride	$189.80		$189.80
OV1GP	$22.19		
OV2GP	$31.25		$31.25
PSA	$49.00		
SCr	$16.00	SCr allocation/period†	$9.60
UA	$22.00	UA allocation/period†	$13.20
	$330.24		**$243.85**
Doxazosin			$94.64
Titration	$92.82		
OV1GP (4 × $22.19)	$88.76		
OV2GP	$31.25		$31.25
PSA	$49.00		
SCr	$16.00	SCr allocation/period†	$9.60
UA	$22.00	UA allocation/period†	$13.20
	$299.83		**$148.69**
Prazosin			$25.48
Titration	$23.52		
OV1GP (3 × $22.19)	$66.57		
OV2GP	$31.25		$31.25
PSA	$49.00		
SCr	$16.00	SCr allocation/period†	$9.60
UA	$22.00	UA allocation/period†	$13.20
	$208.34		**$79.53**
Terazosin			$81.90
Titration	$81.90		
OV1GP (4 × $22.19)	$88.76		
OV2GP	$31.25		$31.25
PSA	$49.00		
SCr	$16.00	SCr allocation/period†	$9.60
UA	$22.00	UA allocation/period†	$13.20
	$288.91		**$135.95**
TURP/ReTURP	$3409.29		
OV1Urol	$39.06		
OV2Urol	$61.87		
OV2GP	$31.25		$31.25
URF	$55.00		
PVR	$95.00		
SCr	$16.00	SCr allocation/period†	$9.60
UA	$22.00	UA allocation/period†	$13.20
	$3724.47		**$54.05**

* For key to abbreviations, see Table 1.

† SCr and UA allocation/period is a method employed to accrue the respective lab costs over the remaining periods after the initial 6 months of therapy with each treatment modality.

Results

In Table 4 the difference between rows one through five demonstrates the expected results of initiating drug therapy with finasteride. From examination of rows one through three in Table 4, two results are

Table 3. Ranges Used in Monte Carlo Simulation

Variable	Minimum	Point Estimate	Maximum
Finasteride efficacy	52%	67%	80%
Alpha-blocker efficacy	57%	74%	88%
TURP efficacy	73%	88%	98%
ReTURP efficacy	25%	50%	75%
Expected efficacy after initial success with given therapy (exception: ReTURP Efficacy)	80%	95%	100%
Finasteride cost	$297.22	$330.24	$363.26
Finasteride continuation	$219.47	$243.85	$268.24
Doxazosin cost	$269.85	$299.83	$329.81
Doxazosin continuation	$133.82	$148.69	$163.56
Prazosin cost	$187.51	$208.34	$229.17
Prazosin continuation	$71.58	$79.53	$87.48
Terazosin cost	$260.02	$288.91	$317.80
Terazosin continuation	$122.36	$135.95	$149.55
TURP cost	$3352.02	$3724.47	$4096.92
TURP continuation	$48.65	$54.05	$59.46
ReTURP cost	$3352.02	$3724.47	$4096.92
ReTURP continuation	$48.65	$54.05	$59.46

appreciated: (1) alpha-blockers were more cost-effective than a TURP after a finasteride failure (compare rows one, two and three to rows four and five); (2) prazosin was the most cost-effective alpha-blocker therapy used after a finasteride failure. The difference between rows four and five is indicative of the cost-effectiveness of alpha-blockers (in this case, prazosin) over a ReTURP after an initial failed course of finasteride and a failed TURP procedure.

Row one of Table 5 demonstrates prazosin to be the most cost-effective of the alpha-blockers. In addition, prazosin is the most cost-effective therapy (Tables 4 and 5) of any path, followed by finasteride, TURP, and a second (Re-) TURP. The difference between rows two and three in Table 5 demonstrates finasteride is more cost-effective than a ReTURP after a failed course of any given alpha-blocker and a TURP procedure. Finally, comparing Tables 4 and 5, the cost-

Table 4. Results for Initial Treatment with Finasteride

Row	Pathway after finasteride failure* -Scheme-	% Success†	C/E‡
1	á - blocker (Prazosin) TURP ReTURP	99.43	$1606.06
2	á - blocker (Terazosin) TURP ReTURP	99.43	$1689.48
3	á - blocker (Doxazosin) TURP ReTURP	99.43	$1705.72
4	TURP á - blocker (Prazosin) ReTURP	99.28	$2488.04
5	TURP ReTURP á - blocker (Prazosin)	97.82	$2658.80

* The "Pathway after Failure" column demonstrates the paths forced along the decision trees (Figure 1). The sequential order in this column indicates the chronological succession of the various therapeutic regimens.

† The "% Success," column demonstrates the % of patients with successful treatment along the respective pathways.

‡ Cost-effectiveness, cost per successful treatment.

Table 5. Results for Initial Treatment with an Alpha-Blocker

Row	Pathway after á - blocker Failure* -Scheme-	Prazosin % Success†	Prazosin C/E‡	Terazosin % Success†	Terazosin C/E‡	Doxazosin % Success†	Doxazosin C/E‡
1	Finasteride TURP ReTURP	99.41	$1154.81	99.41	$1423.43	99.41	$1476.77
2	TURP Finasteride ReTURP	99.49	$1675.42	99.49	$1943.84	99.49	$1997.14
3	TURP ReTURP Finasteride	99.26	$1694.09	99.26	$1963.11	99.26	$2016.52

* The "Pathway after Failure" column demonstrates the paths forced along the decision trees (Figure 1). The sequential order in this column indicates the chronological succession of the various therapeutic regimens.

† The "% Success," column demonstrates the % of patients with successful treatment along the respective pathways.

‡ Cost-effectiveness, cost per successful treatment.

effectiveness of any of the alpha-blockers is greater than that of finasteride.

The AHCPR BPH guidelines assume all the alpha-blockers have the same efficacy,[1] thus, the critical question is whether a clinical situation would occur where finasteride would be more cost-effective than prazosin. To cast light on this question, a Monte Carlo simulation was utilized. Out of 1,000 trials, prazosin was not only more cost-effective than the other alpha-blockers, but more importantly, it was more cost-effective than finasteride in all trials. Thus, when pharmacologic intervention is employed as first-line therapy following watchful waiting, the following inference can be drawn: prazosin is always more cost-effective than doxazosin, terazosin, and finasteride.

Table 6 outlines the most cost-effective step-wise approach in the treatment of BPH. These results depict 36 months of consecutive treatment. The costs are cumulative and reflect the cost per additional patient treated, while the success indicates percent of total patients successfully treated by a particular therapy. For example, when 1,000 patients are started on prazosin therapy after a failed course of watchful waiting, 703 patients would be successfully treated at a cost of $578.15 per patient. Of the remaining 297 patients, 199 patients would be successfully treated with finasteride at a cost of $1,426.53 per each additional patient. Of the final 98 patients, 86 would successfully respond to the TURP and 6 would respond to the ReTURP. The patients successfully treated with TURP would cost $4,321.36 per patient while those treated with ReTURP would cost $7,650.54. Note that included in the ReTURP group would be 6 patients who were not successfully treated.

Of a given population of males greater than 50 years of age with classic symptoms of prostatism and no confounding morbidities, the model predicts that 99.41% of patients would be treated successfully if they were to begin therapy with prazosin and had the listed additional therapies substituted as clinically necessary. Based on 99.41% successful treatment, the final mean cost-effectiveness of the proposed algorithm is $1114.53 for each successful treatment.

Discussion

The elderly population is one of the fastest growing populations in America. This fact, coupled with the reality that symptomatic BPH prompts one in every four men under the age of 80 years to seek treatment, indicates that proven, cost-effective treatment of BPH will be necessary in subsequent years.[1] This study was intended to apply only to males greater than 50 years of age with classic symptoms of prostatism and no other confounding comorbidities. The model incorporated pertinent costs and assumptions for both medical and surgical treatment of BPH from the military payer's perspective.

Table 6. Data Analysis—Cost and Percent Success for Suggested Algorithm

Treatment	Total Cost ($)	Success (%)	Weighted Cost ($)
Prazosin	$ 578.15	70.30%	$406.44
Finasteride	$1426.53	19.90%	$283.88
TURP	$4321.36	8.62%	$372.50
ReTURP	$7650.54	0.59%	$ 45.13
		Total Weighted Cost =	$1107.95
		Total Success =	99.41%
		Total Average C/E =	$1114.53

The AHCPR guidelines were used as the basis of efficacy rates for this study. Again, data not specified in the guidelines were obtained from the current literature or clinical consultant panelist consensus. The sensitivity analysis included the entire AHCPR 90% confidence interval of symptom improvement ± 2% in a uniform distribution, since the actual distribution of the data is not known. This conservative approach incorporated the entire confidence interval of global subjective symptom improvement with an additional two percentage points on both the high and low ends to demonstrate the robust results of the model.

It should be noted that between the study completion and the writing of this manuscript, efficacy data were revised in the finasteride package insert. This reflected a refined response analysis for finasteride that met identical criteria for terazosin market approval. Current finasteride product literature asserts approximately 60% (previous product literature, less than 50%) of patients experience an increase in urinary flow and a 30% or greater improvement in symptoms when treated with finasteride.[17] In light of these new data, it should be noted that there is equivocal evidence correlating BPH symptomatology and quality of life with objective findings such as urine flow and prostate size. This analysis used AHCPR efficacy rates based on a median probability of 67% for symptom improvement. As previously stated, this study's sensitivity analysis incorporated the AHCPR 90% confidence interval of 54% to 78% with a conservative 2% on the low and high range values. Thus, change in the finasteride product literature does not effect the validity of this study's results.

The efficacy of each therapy in the model was assessed after 6 months. This time frame was used due to the structured nature of a decision tree methodology which required a measure of consistency between the various treatment arms. The clinical reason for this time frame is that the recommended assessment of finasteride efficacy commonly ranges between 6 and 12 months, whereas alpha-blocker efficacy is frequently assessed at 6 months (or even shorter) after initiating therapy. Thus, to preclude distortion, all therapies were compared to one another after a period of 6 months.

This method causes a bias in favor of the alpha-blockers. If the alpha-blockers were evaluated in as short as 4 to 6 weeks, then the patients who do not respond to alpha-blockers would be switched earlier to finasteride. This simplifying assumption translates into an increase of $23 in the costs of an alpha-blocker compared to finasteride, an inconsequential increase. The impact of earlier evaluation of alpha-blocker efficacy is to move up the timetable of the 26% of patients who do not respond to an alpha-blocker. Because this shifting in time is so small there is no appreciable impact except that 67% of these 26% (those successfully treated with finasteride) would incur an additional 4 to 5 months of finasteride treatment at the end of the study. This cost must then be rolled back through the decision tree, in addition to being discounted since it is incurred 36 months in the future. The cost of finasteride is $189 per six month period or $157 for five months. This translates into a net present value (discounted cost) of $135. This discounted cost for the 67% of the 26% is $23 (67% × 26% × $135 = $23).

Government prices were used for drug costs. Costs of outpatient office visits were adapted from CPT codes and the RBRVS. Inpatient surgical costs were based on Medicare reimbursement schedules. It should be pointed out that actual costs to the federal government were not clear in all cases. An additional point regarding cost concerns mortality. Sufficient mortality data are not available in the medical literature. It is speculated, however, that since the preponderance of mortality occurs secondary to surgery, the ranking would not have changed, but the costs of surgical procedures would have been higher and their effectiveness less. The final recommendation of using drug therapy first and delaying surgical treatment would remain the same.

A Monte Carlo analysis examined the "robustness" (how well results withstand changes in assumptions) of the model. The more robust a model, the less it is affected by changes in assumptions and variables, and the more confidence in its results. A typical simulation entails a thousand or more trials, with a unique solution for each trial based on the random assignment of values to each variable within a range defined by the literature. Analyzing the distribution of results allows inferences to be made as to how well the original solution withstands changes in the variables. In a robust model, only a few, if any trials, will demonstrate results significantly different from the point estimates. On the other hand, a model very sensitive to variations in assumptions will drastically change results during the simulation. For example, in a model whose point estimates predict option "A" to be the best, the simulation may actually demonstrate that several other options (e.g., options "B," "C," etc.) are better as the conditions vary.

The Monte Carlo simulation of this model demonstrated that prazosin was always more cost-effective than doxazosin and terazosin during the simulation. Additionally, prazosin was always more cost-effective than finasteride. This demonstrates the model to be very robust since changing the variables did not change the results. Thus, the results are valid for a large range of assumptions.

Doxazosin tablets are scored, thus it is possible a patient could split tablets and decrease the cost per dose. Because a large cost difference exists between doxazosin and the less expensive prazosin capsules, the practice of splitting tablets would not substantially change the cost-effectiveness range between these two agents. Doxazosin tablets and terazosin capsules are similar in cost, thus the practice of splitting tablets would affect the cost-effectiveness ranking between these agents in favor of doxazosin. No data are available describing the patient compliance or efficacy with tablet-splitting regimens.

Compliance was assumed equal for all drug therapies included in the study. It is possible this assumption biases prazosin since this drug is dosed twice daily while the other medications are dosed once-daily. However, several reports have not shown a notable difference in once versus twice daily dosing.[35-37] For instance, Rudd[35] noted a 73% compliance rate with once-daily dosing and a 70% compliance rate with twice-daily dosing. Furthermore, it could be expected that patients with symptoms of BPH may be motivated to remain compliant. Finally, the robustness of the Monte Carlo sensitivity analysis demonstrates that the assumption of equal compliance between the different treatment regimens has little impact. Differences in compliance rates will have little impact unless those differences are extremely large, something not supported in the literature.

There is some question of prazosin having a higher side effect profile, potentially lower compliance rate, and limited efficacy in treating BPH. However, these issues are not well supported in the literature. Clinical studies and available package inserts document prazosin as having a similar side effect profile when compared to the other selective alpha-blockers, when used in doses for the treatment of BPH in normotensive men.[18-20,27-29,38] Additionally, several randomized, placebo-controlled trials have established prazosin's efficacy in the treatment of BPH.[30-34] Prazosin, like all alpha-blockers, should be initiated at the lowest possible dose and titrated slowly as needed to achieve an adequate response.[15,16,21]

Although not demonstrated in published clinical trials evaluated by AHCPR, it is theoretically possible one alpha-blocker may be superior to other drugs of its class. Additionally, one or more alpha-blockers may be effective in severe symptomatology in addition to accepted effectiveness in mild to moderate BPH. For instance, the Hytrin Community Assessment Trial (HYCAT), a randomized, multi-center, placebo-controlled study that assessed 2,084 patients, was used to evaluate the clinical effectiveness and cost-effectiveness of Hytrin® in the treatment of men with symptomatic BPH.[38] This study assessed men with moderate-to-severe prostatism who were at least 55 years of age (mean age 66 years) with a minimum AUA score of thirteen. The one-year study reported Hytrin® to be approximately twice as effective as placebo. This study also demonstrated the drug's efficacy in severely symptomatic patients. This study suggests alpha-blockers for the treatment of severe BPH, additional clinical trials extending beyond one year and comparing other alpha-blockers would be helpful.

Another valid question regarding efficacy refers to a possible interdependence between BPH therapies. In the model, each therapy was independent of previous therapies. One could speculate a specific therapy used before another might modify the succeeding therapy's efficacy rate or BPH complication rates; however, this is not fully substantiated. Results of the sensitivity analysis indicate this may not be a significant issue.

While current literature supports an acceptable safety profile of finasteride, its true clinical efficacy appears less conclusive, with the suggestion that finasteride is more efficacious in men with larger prostates.[39,40] Clinical efficacy is represented by results obtained during randomized clinical trials where strict controls, including adherence to dosage regimens can be monitored. In contrast, clinical effectiveness is represented by a combination of efficacy with compliance to more accurately represent real world clinical situations where monitoring may be absent.

As part of the sensitivity analysis, the efficacy of finasteride was assumed to be 100%; all patients receiving finasteride had symptom improvement. The results demonstrate the apparent paradoxical, yet common sense nature of cost-effectiveness analysis. In this situation, as the efficacy of finasteride increases, the cost-effectiveness of finasteride compared to prazosin (or the other alpha-blockers) actually becomes worse. This result occurs because the cost of finasteride is greater than any possible advantage it could have in efficacy compared to prazosin. Therefore, as more patients are successfully treated first with finasteride, the total cost increases faster than the total effectiveness. Even in the face of a 100% efficacy for finasteride, it is even more cost-effective to treat as many people as possible with prazosin, before switching to the hypothetically more efficacious finasteride for those patients that fail the lower cost and less efficacious prazosin.

When comparing the reported cost-effectiveness ratio for prazosin in Table 4 with Table 6, a discrepancy can be noted. Although the percent of treatment success is equal in both tables, disparity arises in the two reported cost-effectiveness ratios. The discrepancy was attributed to the fact that Table 4 accounts for all patients, whereas Table 6 accounts for 99.41% who were successfully treated. If treatment failures were accounted for in Table 6, the total average cost-effectiveness would be an expected $1159.67. The $4.86 difference is rounding error.

BPH Treatment Guidelines

Based on the results of this study, the Pharmacoeconomic Center recommends the following treatment guidelines for mild to moderate BPH patients who have failed watchful waiting. An algorithm for the treatment of mild to moderate BPH is illustrated in Figure 2.

1. Unless clinically contraindicated, all patients should first receive a trial with prazosin at an appropriate dose. The most cost-effective approach to treating BPH is prazosin even if some patients cannot tolerate the occasional side effects.
2. For patients who can not tolerate prazosin or who fail to respond to it, then terazosin is a viable cost-effective alternative.
3. Finasteride is the least cost-effective therapy, and should be considered only in those patients in whom alpha-blockers are contraindicated, or in those patients who fail an adequate trial with prazosin or terazosin.
4. Doxazosin, at present, provides no advantage compared to prazosin or terazosin. This situation could change if tablet breaking strategies were shown to be effective.

Preferred Drug List

Rank	Drug	Cost per Successful Treatment (Average C/E)
1	Prazosin	$1,154.81
2	Terazosin	$1,423.43
3	Doxazosin	$1,476.77
4	Finasteride	$1,606.06

Tri-Service Formulary (TSF) Selection

The results of the disease state analysis of benign prostatic hyperplasia demonstrate that the alpha-blockers are the most cost-effective pharmacologic therapy, with prazosin more cost-effective than other alpha-blockers. Based on this analysis prazosin is added to the Tri-Service Formulary. Terazosin, the next most cost-effective alpha-blocker, is currently on the TSF for hypertension, but should be considered for those patients with BPH who cannot tolerate prazosin. Terazosin will remain on the TSF.

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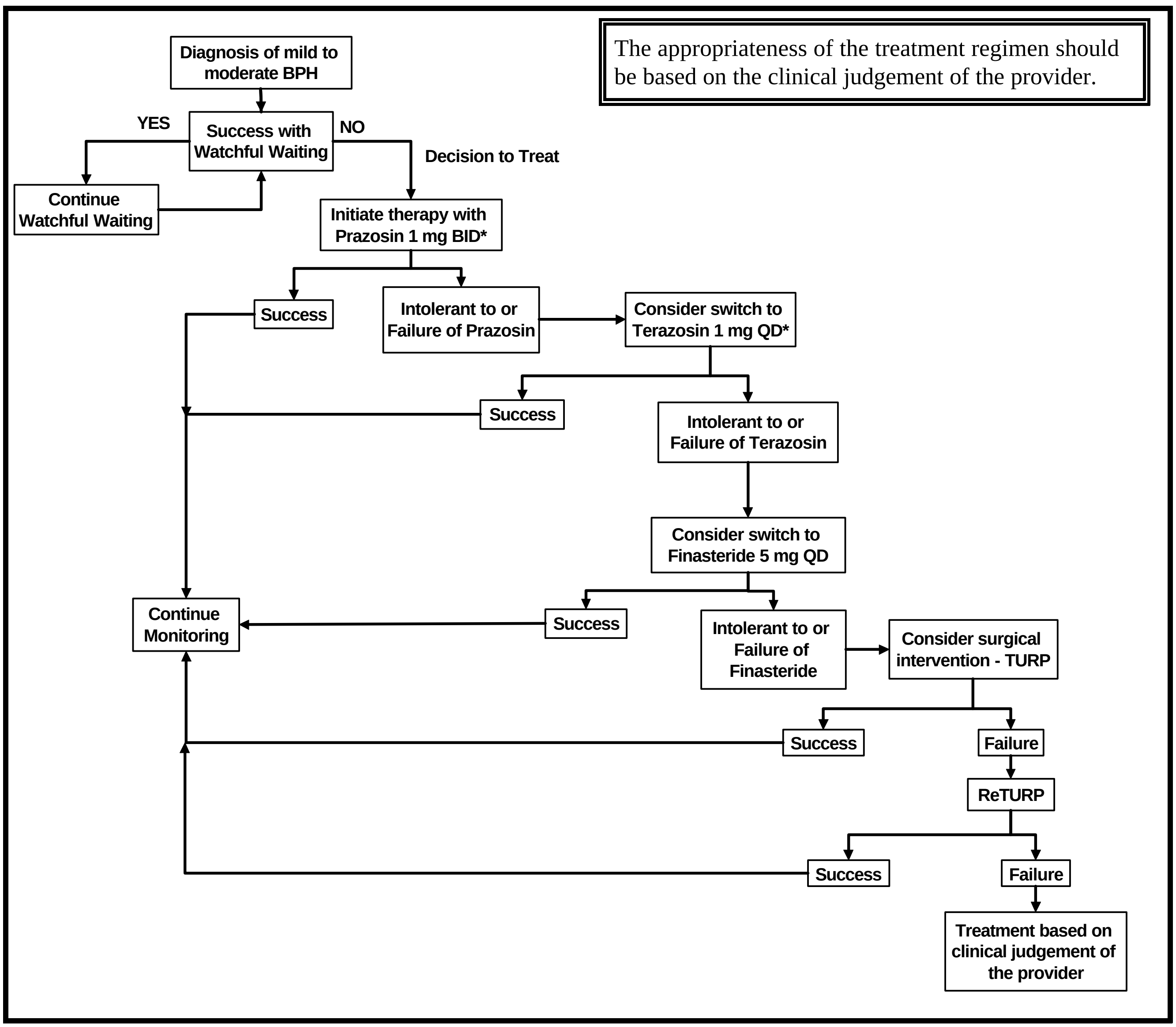
Figure 2. BPH Treatment Algorithm



* Prazosin should be initiated at the lowest possible dose (1 mg bid) with the first dose administered at bedtime to minimize the risk of postural hypotension. The prazosin dose should be titrated every 7 to 14 days as tolerated to achieve a response. Terazosin should be initiated at a dose of 1 mg at bedtime to minimize the risk of postural hypotension. The terazosin dose should be titrated every 7 to 14 days as tolerated to achieve a response.

DRUG USAGE EVALUATION MONITORING FORM

DISEASE STATE Benign Prostatic Hyperplasia ____ DRUG ____

SURVEY PERIOD: FROM: ____ TO: ____

COLLECTED BY: ____ DATE OF COLLECTION: ____

ATTENDING PHYSICIAN ____ SERVICE ____

PATIENT NAME ____ SSN ____ AGE ____

SEX ____ WEIGHT ____ ALLERGIES ____

ELEMENT	STD*	MET STD	COMMENT
1. Patient: • Clinical improvement in mild to moderate symptoms of BPH (frequency of urination, nocturia, urgency, and urge incontinence, etc.).	100%	Y/N	
2. Therapy: • Drug therapy initiated with an alpha-blocker after unsuccessful, watchful waiting. ➤ Initiate treatment with prazosin (1 mg - 5 mg BID) • Intolerance to prazosin or failure ➤ Initiate treatment with terazosin (1 mg - 10 mg QD) • Failure of terazosin ➤ Initiate treatment with finasteride (5 mg QD)	100% 60% 10% 20%	Y/N Y/N Y/N Y/N	
3. Monitoring: • Initial prostate specific antigen. • Initial and periodic serum creatinine and urinalysis.	 100% 100%	 Y/N Y/N	
4. Less than optimal outcome (select category if present): a. Inappropriate drug regimen. b. Non-compliant behavior by patient. c. Patient allergy/idiosyncratic reaction. d. Complication unrelated to drug therapy. e. Inappropriate monitoring of pharmacotherapy (i.e., drug-drug or drug-food interactions).	30%	Y/N	

* Standard to be adjusted by MTF Pharmacy & Therapeutics / Drug Utilization Evaluation Committee.

Tri-Service Formulary Quick Reference Guide

Antimicrobials / Antifungals
*amoxicillin oral suspension and caps
*Bactrim™/Septra® susp and tabs
*dicloxacillin oral
*doxycycline 100 mg caps
*erythromycin oral suspension and tabs or caps
*erythromycin/sulfisoxazole susp
*griseofulvin 125 mg tabs
*isoniazid 300 mg tabs
*metronidazole 250 mg tabs
*nystatin oral suspension
*penicillin VK susp and 250 mg tabs
*rifampin 300 mg caps
*tetracycline 250 mg caps

Antibiotics-EENT
*Cortisporin® Otic Suspension
*gentamicin ophth. soln. 0.3%
*Neosporin® Ophth. Solution
*sulfacetamide ophth. oint. 10%

Antivirals
acyclovir 200 mg caps

Anthelmintics
mebendazole 100 mg chew tabs

Antiulcer Drugs
*amoxicillin oral
*bismuth subsalicylate 262 mg tabs
*metronidazole 250 mg tabs
*tetracycline 250 mg caps

GERD Agents
cisapride 20 mg tabs
omeprazole 20 mg caps

Other GI Agents
*dicyclomine tabs or caps
*Donnatal® tabs
*sulfasalazine 500 mg tabs

Anti-diarrheals
*loperamide 2 mg tabs or caps

Genitourinary Agents
*oxybutynin 5 mg tabs
*phenazopyridine 100 mg tabs
*prazosin 1 mg, 2 mg, 5 mg caps
terazosin caps

Gout Agents
*allopurinol tabs
*probenecid 500 mg tabs

Muscle Relaxants
*diazepam 5 mg tabs
*methocarbamol 500 mg tabs

Oral Corticosteroids
*prednisone 5 & 20 mg tabs
prednisone oral soln 5 mg/5 mL
prednisolone oral soln 15 mg/5 mL

Nasal Corticosteroids
*beclomethasone nasal inhaler

Asthma Agents
*albuterol oral inhaler
flunisolide oral inhaler
triamcinolone oral inhaler
*theophylline liquid 80 mg/15 mL
SloBid™ Gyrocaps 50, 200, 300 mg

Antihistamines / Decongestants
*Actifed® tabs
*chlorpheniramine 4 mg tabs
*chlorpheniramine syrup
*Dimetapp® Elixir
*Dimetapp® Extentabs
*diphenhydramine caps
*diphenhydramine syrup
*hydroxyzine syrup
*hydroxyzine tabs
*oxymetazoline nasal spray
*pseudoephedrine 30 mg tabs

Anticonvulsants
†Dilantin® Infatabs 50 mg
†Dilantin® Kapseals 100 mg
*phenobarbital elixir 20 mg/5 mL
*phenobarbital 30 mg tabs
*primidone 250 mg tabs
†Tegretol® 200 mg tabs

Anticoagulants
warfarin 5 mg tabs

Diuretics
*furosemide 40 mg tabs
*hydrochlorothiazide tabs
*Maxzide® tabs
*spironolactone 25 mg tabs

Vasodilators
*isosorbide dinitrate 10 mg tabs
nitroglycerin sublingual tabs

Lipid Lowering Agents
colestipol powder
*niacin tabs
pravastatin 10 mg, 20 mg, 40 mg tabs

Hypotensive / Cardiac Drugs
*atenolol tabs
*clonidine tabs
†Lanoxin® 0.25 mg tabs
lisinopril tabs
*propranolol 10 & 40 mg tabs
*quinidine gluconate 324 mg tabs
*quinidine sulfate tabs
terazosin tabs
*verapamil long-acting tabs

Electrolyte Replacement
*potassium chloride slow release tabs or caps

Diabetic Agents
*human insulin, regular & NPH

NSAIDS / Analgesics
*acetaminophen drops, elixir, and 325 mg tabs
*aspirin, enteric-coated 325 mg tabs
*ibuprofen susp and 400 mg tabs
*indomethacin 25 mg caps
*Tylenol #3® tabs

Migraine Agents
*Cafergot® tabs
*Fiorinal® tabs
*Midrin® caps

Attention Deficit / Narcolepsy Agents
*methylphenidate 10 mg tabs
*methylphenidate sustained release 20 mg tabs

Contraceptives
LoOvral®
*Norinyl 1+50®, Ortho-Novum 1/50®
*Ortho-Novum 1/35®, Norinyl 1+35®
Ortho-Novum 7/7/7®
Ovral®
Triphasil®/Tri-Levlen®

Estrogens / Progestins
conjugated estrogens 0.625 mg tabs
conjugated estrogen vaginal cream
*medroxyprogesterone 10 mg tabs

Thyroid / Antithyroid Agents
*propylthiouracil 50 mg tabs
†Synthroid® 100 mcg (0.1 mg) tabs

Topical Agents
*bacitracin ointment
*hydrocortisone 1% cream
*miconazole 2% topical cream
Sebutone® shampoo
*Selsun® shampoo

Vaginal Antifungal Agents
clotrimazole 100 mg vaginal tab

Vitamins & Minerals
*ferrous sulfate concentrated soln. 125 mg/mL
*ferrous sulfate 325 mg tabs
*pyridoxine 50 mg tabs

Miotics
*pilocarpine ophth. solution

Miscellaneous
insect sting kit
InspirEase® spacer

**** generic products are available***
† sole source item

Brand names are included for example only and are not meant to imply the recommendation of a specific product except for those products designated as sole source items by the Pharmacoeconomic Center.